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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/892,864	06/28/2001	Keiichi Yokoyama	209524US0 CONT	3226

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EXAMINER
PATTERSON, CHARLES L JR

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/892,864	YOKOYAMA ET AL.	
	Examiner	Art Unit	
	Charles L. Patterson, Jr.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,41-43,72,73 and 75-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,41-43,72,73 and 75-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 18, 34-36, 73 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The previous rejection of claim 1 is hereby dropped due to applicants arguments. Although the Bailer, et al. reference submitted does not appear to address the term "neutral pH", it is deemed that applicants disclosure of acidic pH as being pH 2-7 and neutral pH as being pH 5.8-8.5 is limiting on the claims.

Claim 18 states that "prior to step (b) [of claim 1], the...medium...is diluted to a concentration of not more than 10 mg/ml". Step (b) of claim 1 is now drawn to a dilution of 5 to 400 fold. It is not clear whether the dilution of the instant claim is intended to be in addition to that of the amended claim 1.

Claim 34 is confusing and indefinite in the recitation of "the surfactant". There is no antecedent basis for this phrase in claim 21. Apparently claim 33 was intended.

Claim 35 is confusing and indefinite in the recitation of "(c) centrifuging the aqueous medium of (c)". The instant claim adds step (c) to claim 1, which already has a step (c).

Claims 36 and 73 are incorrect in the recitation of "an structure" in line 2, which apparently should be "a structure".

Claim 78 is indefinite in the recitation of "Claim 26". Claim 26 is drawn to a process, not a transglutaminase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and

use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38, 41-43, 73, 73 and 75-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing a transglutaminase using the conditions in Examples 1-16, does not reasonably provide enablement for producing the transglutaminase under the requirements of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. This rejection is repeated for the reasons given in the last action. Applicants arguments have been carefully considered but do not overcome the instant rejection.

Applicants state that this "is described in the specification on pages 10-12". These pages recite broad ranges of pH, concentrations, temperatures, dilutions, etc., but do not give any results for these wide ranging conditions. As stated previously, examples 1-16 teach that transglutaminase was denatured in 8 M urea and 20 mM DTT, then the pH was adjusted to 4.0 in buffer containing the same 8 M urea and 20 mM DTT, cooled to 5° C and then the urea concentration was lowered and the pH adjusted to 6.0. The specification does teach dilution of the denatured enzyme, but the dilution is 1.25-fold in examples 1 and 4-10, 250-fold in examples 2 and 3 and 50-fold in example 11. This does not approach the "400-fold" in amended claim 1.

Claim 75 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is

repeated for the reasons given in the last action. Applicants arguments have been carefully considered but do not overcome the instant rejection.

The examiner asked in the previous action whether the enzyme claimed in claim 75 was meant to the "intermediate state" enzyme, i.e. denatured enzyme at acid pH. Applicants did not answer this question, but since they referred to example 16 in their answer it is presumed that this is true. There is apparently nothing in the instant specification that teaches that this intermediate state enzyme has "a molecular weight of 36,000-40,000 as measured by SDS-polyacrylamide gel electrophoresis", absent a convincing showing to the contrary.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, 13-14, 19, 21-38, 41-43, 72-73, 76-83 and 85-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ejima, et al. (AY). This rejection is repeated for the reasons given in the last action. Applicants arguments have been carefully considered but do not overcome the ins-

tant rejection. Applicants argue that the method taught by the instant reference does not include dilution and the amended claims include a dilution step. In the paragraph spanning columns 1 and 2 on page 302 it is taught that:

> "The pellet of inclusion bodies was solubilized in 6M GdnHCl (13.8 mg/mL), adjusted to pH 5.5 with HCl and allowed to stand for 2 h at room temperature. Solubilized hIL-6 (1.5 mL) was rapidly diluted 10-fold to 1.38 mg/ml with 10 mM Tris-HCl, pH 8.5..."

This meets the dilution step added to claim 1. It would have been obvious to one of ordinary skill in the art to treat denatured transglutaminase according to the same methods used in the instant reference with the expectation that biological activity would be restored. Anything not specifically taught in the instant reference would have been obvious, absent a convincing showing to the contrary.

Claims 38, 41-43, 72-73 and 79-81 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kawai, et al. (AW). The instant reference teaches in the paragraph spanning pages 831-832 the centrifugation of transglutaminase that had been denatured with guanidine-HCl and then the subsequent dialysis and centrifugation of this solution. This would be "an intermediate transglutaminase". It then teaches the addition of factor Xa, which supposedly digests a part of the transglutaminase off. This step forms a "higher-order native state structure exhibiting enzymatic activity. If all the requirements of the instant claims are not met by the instant reference, it is maintained that they would have been obvious, absent convincing proof to the contrary.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 703-308-1834. The examiner can normally be reached on Monday - Friday, 7:30-4:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone number is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
June 23, 2003